The infant's susceptibility to certain toxic effects which are seen most commonly and in severest form with the broad-spectrum antibiotics must always be considered when deciding upon the most suitable antibiotic. In order to reduce to the minimum the number of babies receiving broad-spectrum antibiotics when narrow-spectrum antibiotics would be as effective, the administration of broad-spectrum antibiotics should be limited to cases which fall into one of the following categories: (1) when the infecting organism is insensitive to bactericidal antibiotics; (2) where temporary cover is necessary while awaiting the bacteriological diagnosis; and (3) when the bacteriological investigations have failed to demonstrate a pathogenic organism, and the nature of the causative organism remains obscure.

The modifications in antibiotic therapy which the conditions of infancy dictate may not in themselves seem great. They do, however, demand of the physician greater attention to exact bacteriological diagnosis, greater care in the choice of drug and dosage, and the avoidance of delay in bringing effective treatment to bear. They may also involve some inconvenience in that injections are more often required. Nevertheless, it is by such means that improvement in the present mortality figures must be sought.

Whatever the extent of the progress that can be brought about by these means there is little doubt that great progress could be achieved if we had the knowledge and ability to raise the efficiency of host resistance in infancy.

Summary

Successful treatment of infections with the aid of modern antibacterial drugs depends *inter alia* upon healthy host resistance. When host resistance is depressed to any great extent the therapeutic effect of antibacterial agents may be nullified and the clinical response unsatisfactory.

In contrast to the state in old age, or resulting from prolonged illness or cortisone therapy, poor resistance in infancy is primarily a manifestation of the immaturity of the various defensive mechanisms, rather than a depression of previously normal resistance. Characteristically, the phagocytic ability of the leucocytes of infants is less than that of the cells of adults. The antibody response may be slow and incomplete through lack of previous stimulation, and may also be affected by the presence of circulating maternal antibody. It is, moreover, usual to find the response delayed and incomplete, even in normal infants below the age of 2 months. After this age the level of the gamma-globulin in the serum is still abnormally low and may well exert an adverse influence on defence, though at present the exact significance of this finding is uncertain.

Taken together, these deficiencies go much of the way to explain the inability of infants to limit spread of infection and to bring about the ultimate destruction and eradication of the invading micro-organisms. The rapid dissemination of bacteria throughout the body makes prompt control a point of special and often decisive therapeutic importance, which must be taken into account when deciding upon the most advantageous method and route of administration. The infants' poor killing power that permits bacteria suppressed by bacteriostatic agents to remain viable makes it necessary to employ antibiotics which are themselves actively bactericidal.

When treating infections of infants the physician has a greater responsibility to prevent further impairment of host resistance resulting from additional stresses such as metabolic disturbance, superinfection, or direct toxicity of the antibiotic on tissue cells. In this respect narrow-spectrum antibiotics are usually less injurious

and therefore safer in practice than those whose spectrum is wide. It follows that the best antibiotics for use in infancy are those like penicillin, which combine narrow antibacterial range and bactericidal action. Not only is the need for discrimination in selecting the correct antibiotic more pressing but also the more serious consequences, particularly those due to suboptimal dosage, make care and accuracy in prescribing of greater and more decisive importance in infancy than at any other age.

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LYMPHATIC CIRCULATION STUDIED WITH RADIOACTIVE PLASMA PROTEIN

BY

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In this investigation plasma protein labelled with radioactive iodine (^{131}I) (R.P.P.) has been used to study the lymphatic circulation in normal subjects and in patients suffering from lymphoedema.

Three questions were considered. (1) Are extra-vascular protein molecules removed solely by the lymphatics or does absorption by the blood capillaries occur? (2) Does the absorption of protein from the subcutaneous tissues of lymphoedematous patients differ from that in normal subjects? (3) Could the removal rate of R.P.P. from the subcutaneous tissues be used as a test of lymphatic function in clinical practice?

Six normal subjects and ten patients suffering from lymphoedema were investigated. Similar determinations were made in normal rabbits and in rabbits with a limb rendered oedematous by acute lymphatic transection (Reichert, 1926). In addition, the clearance rate of crystalloid solution iodide (^{131}I) from the subcutaneous tissues was determined in some patients and animals.

Experimental Method

The method of Wormall, Francis, and Mulligan (1951) was used to prepare R.P.P. solutions of high specific activity by labelling human or rabbit autogenous serum protein with radioactive iodine (^{131}I). Small volumes of solutions

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and radio-iodine of high specific activity were used so as to give a final preparation of 1 to 2 ml. of 2% protein solution containing 0.5 to 1 millicurie of ^{131}I per ml. ^{131}I in the form of iodide was removed by dialysis with normal saline, changed every half-hour, and mechanically stirred. To reduce bacterial activity during this part of the preparation the dialysis was carried out in a refrigerator. The preparation was then sterilized by filtration through an M.S.E. centrifugal Seitz filter and tested bacteriologically before use.

Injectations and Observations in Human Subjects

The R.P.P. solution was injected subcutaneously into the limbs of the patients and normal subjects. It was considered important to keep the volume of R.P.P. injected as small as possible in order to minimize disturbance of tissue tension, and usually 0.1 ml., containing about 100 microcuries of ^{131}I , was used. When the specific activity of the R.P.P. was low and a larger volume had to be used, several injection sites were employed, close enough together to be regarded as a single site for counting purposes. No more than 0.1 ml. of R.P.P. solution was injected at any one site.

In the early stage of this investigation the counting rates over the areas surrounding the injection site were observed with a shielded Geiger counter of small aperture held in contact with the skin. Although this method demonstrated well the local diffusion of R.P.P. around the injection site, it was unable to separate the effect of local diffusion into the tissues from that of actual removal from the limb. For this reason it was necessary to discard the results of local counting obtained in the first seven patients. In the last three patients to be investigated and in six normal subjects this difficulty was overcome by using a counter of larger aperture, held at a distance of 22 cm. from the skin.

The arrival of R.P.P. in the blood was estimated in five patients and four normal subjects by taking 3-ml. samples of venous blood from an arm vein. Frequent specimens were obtained during the first 12 hours and sampling was continued at intervals for seven days. The radioactivity of each blood sample was measured by plating 1 ml. into 1-in. (2.5-cm.) planchettes and counting with an end-window Geiger counter in a lead castle. The diagnosis in four of the patients in this group was lymphoedema praecox of the legs. The remaining patient had an oedematous arm following invasion of the axillary nodes by carcinoma of the breast. One patient had unilateral oedema, and her normal leg was also studied and included in the normal control group.

Injectations and Observations on Rabbits

Two groups of animals were used—transected and normal. In the transected animals a soft-tissue transection of the thigh, except for the main blood vessels, was carried out before the R.P.P. injections. In these animals the R.P.P. was injected under the skin of the paw of the transected leg.

Counting over the injection site was done using a small unshielded Geiger counter in a thin brass case. The counter was held in a wooden jig so that its axis lay about 2 cm. from the skin and parallel to the paw.

Blood specimens were obtained by means of a "polythene" tube inserted in the superior vena cava via the jugular vein. 1 ml. of each blood specimen was placed on a planchette, dried, and assayed in the same way as the human blood.

The completeness of the lymphatic division was tested by injection of patent blue (Kinmonth, 1952) when the transection was performed and also at the end of the investigation.

Experimental Results in Human Subjects

Results of Local Counting over the Injection Site

The observations with the small-aperture counter, after correction for natural background and the physical decay of the radioactive material, and after an approximate correction for the imperfect collimation of the counter, were used to

plot contours of equal activity. These results indicated in a general way the diffusion of the injected R.P.P. through the tissue. It was found that the size of the diffusion area after a given time was greater in the more oedematous limbs. It is also of interest to note that in all cases of lymphoedema the point of maximum activity gravitated appreciably towards the most dependent part. This movement was usually smaller in normal legs.

With this counting technique, however, it was found that the true removal of R.P.P. from limbs was masked by the effects of diffusion. A semilogarithmic plot of the maximum counting rate against time gave a curve instead of a straight line, which would correspond to a simple removal process. A detailed analysis of this curve, to separate the diffusion and disappearance effects, was thought not to be practicable. In later investigations a counter was used with a large aperture held at a sufficiently great distance to cover the whole of the diffusion area. Readings with this counter over the injection site could then be fitted to a single exponential decay, giving a straight line in a semilogarithmic plot even with observations extending over about 50 hours. The slope of this line gives the mean removal rate of the R.P.P. from the injection site, and these values are given in Table I. In this table both groups are arranged in descending order of

TABLE I.—Results of Local Counting Over Injection Site in Human Subjects

Subject	Degree of Physical Activity	Removal Rate of R.P.P. (Percentage of Dose Removed per Hour)
<i>Control Group</i>		
J.R.	Very active	3.9
F.S.	Active	2.2
F.B.	Slight	1.2
M.A.H. ..	Bed	2.5
E.W.H. ..	"	1.0
E.J.	"	1.7
Mean		2.2±0.4
<i>Lymphoedematous Group</i>		
V.S.	Active	1.45
E.J.	Slight	1.06
L.A.P. ..	"	1.7
Mean		1.4±0.2

physical activity, and in addition the lymphoedematous group is tabulated in order of decreasing severity of lymphoedema.

The results show that the clearance rate of R.P.P. in normal subjects is influenced by physical activity and that there is no significant difference in the removal rate in control subjects during bed rest and in active patients with lymphoedema. The mean values of the removal rate in the two groups show no significant difference, but the results suggest that clearance of R.P.P. is slower in patients with lymphoedema than in active normal subjects.

The following conclusions were drawn from the findings of local counting over the injection site in normal control subjects and in patients with lymphoedema. (1) A wide subcutaneous diffusion of the injected R.P.P. occurs around the injection site. This local diffusion is influenced by gravity and is greater in the lymphoedematous patients than in the normal controls. (2) The removal rate of R.P.P. in normal subjects is increased by physical activity. (3) The removal rate of R.P.P. from the limb is greater in normal active subjects than in the lymphoedematous patients.

Measurements of Blood Specimens

The rise of radioactivity in the blood following the injection of R.P.P. for a typical case in the control group is shown in Figs. 1 and 2. Correction has been made for the natural decay of the ^{131}I . Fig. 2 has an expanded scale and shows the result during the first few hours after the injection. It is seen that after an initial rise and flattening the curve increases steeply; it then reaches a maximum and falls slowly owing to the removal of the R.P.P. from the blood.

The observed initial rise and flattening of the curve is attributed to the presence of traces of ^{131}I iodide in the injection solution. This is based on the blood activity curve of a control subject who received a subcutaneous injection of R.P.P. containing a known proportion of ^{131}I as iodide. From this observation a correction could be made for that fraction of the observed activity corresponding to iodide

FIG. 1.—Appearance in the blood of R.P.P. injected subcutaneously into the leg of a normal subject.

FIG. 2.—Early portion of the curve shown in Fig. 1 on an expanded time scale. After an initial rise, a plateau is formed and is followed at 50 minutes by a further steady rise in R.P.P. concentration in the blood.

activity is obtained from the initial slope of the curve and expressed as the percentage of the injected dose per ml. of blood per hour. The values found for the controls and for lymphoedematous cases are summarized in Table II.

In Table II the subjects in the control group are analysed in descending order of degree of physical activity, and it is noticeable that the initial rate of rise corresponds closely to this. The following conclusions were drawn from these estimations of the appearance in the blood stream of the injected R.P.P. in normal control subjects and in patients with lymphoedema. (1) There is a delay in time of from 0.5 to 3.25 hours following the subcutaneous injection before the R.P.P. can be detected in the blood. (2) This delay is greater in patients with severe lymphoedema than in the normal control subjects. (3) The initial rate of rise of R.P.P. content in the blood is greater in the normal control subjects than in the patients with lymphoedema. (4) In normal subjects the initial rate of rise of R.P.P. content in the blood is increased by physical activity.

Experimental Results in Rabbits

Results of Local Counting over the Injection Site

In six normal animals R.P.P. was injected subcutaneously into a hind paw and the counting rate observed over the injection site. The counting rate was found to decay

exponentially and the removal rate of R.P.P. was calculated in the same manner as in the human investigations. Similar measurements were made in five animals with transection of lymphatics in the injected limb. It was found that the removal rate of R.P.P. as determined by local counting did not differ significantly in the control and transected group of animals. Further investigation showed that a high local concentration of R.P.P. was occurring at the site of transection around the cut end of the lymphatics. Thus the R.P.P. was being removed from the paw only to be dumped at the site of the transection, and a true removal rate of R.P.P. from the limb could not therefore be determined.

After subtracting the iodide fraction it was found that there was an appreciable delay before the residual activity—that is the protein-bound contribution—became significant. This delay, as well as the rate of the subsequent rise of the activity in the blood, are suggested as criteria of the efficiency of the lymphatic system. The initial rate of rise of

activity is obtained from the initial slope of the curve and expressed as the percentage of the injected dose per ml. of blood per hour. The values found for the controls and for lymphoedematous cases are summarized in Table II.

FIG. 3.—Appearance in the blood of R.P.P. after subcutaneous injection into a normal leg. The observed points have been corrected for iodide contamination of the R.P.P. and there is a delay period of approximately 50 minutes before the R.P.P. contribution becomes detectable.

TABLE II.—Estimation of Arrival in Blood of R.P.P. Injected Subcutaneously in Human Subjects

Subject	Initial Delay (in Hours)	Initial Rate of Rise of Radioactivity in Blood. ($10^{-4}\%$ of Dose ml. of Blood/Hour)
<i>Control Group</i>		
J.R.	0.5	9.3
F.S.	0.9	6.3
F.B.	1.0	2.5
E.W.H.	0.7	1.6
E.J.	0.8	0.8
Mean	0.8 ± 0.1	4.1 ± 1.6
<i>Lymphoedematous Group</i>		
V.S. } Severe . . .	2.1	0.33
E.J. } oedema . . .	1.45	0.65
L.A.P. }	3.25	0.4
E.K. } Slight . . .	0.6	0.7
G.L.M. } oedema . . .	0.5	1.7
Mean	1.6 ± 0.5	0.56 ± 0.08

Measurements of Blood Specimens

The ^{131}I content of the blood in the control group was found to vary with time in the same way as in the human subjects—that is, it showed a rapid initial rise to a plateau followed by a further rise. Corrections for the small fraction of ^{131}I injected as iodide were based on observations of the activity in the blood of a rabbit injected with ^{131}I in the form of sodium iodide.

In those animals, however, whose lymphatics had been transected the variation of the ^{131}I blood content with time had a different character, as is shown in Fig. 4. It is seen that the significant difference between this analysis and that of Fig. 3 is that the R.P.P. component shows no initial delay. The results obtained for these transected animals and the control group are summarized in Table III,

FIG. 4.—Appearance in the blood of R.P.P. injected subcutaneously into the paw of a rabbit in which acute lymphoedema had been produced by lymphatic transection. The initial part of the curve is shown with the correction for free iodide. The symbols are as for Fig. 3. There is no delay before the R.P.P. contribution becomes detectable in the blood.

TABLE III.—*Estimation of Arrival in Blood of R.P.P. Injected Subcutaneously in Rabbits*

Rabbits	Initial Delay (in Hours)	Initial Rate of Rise of Radioactivity in Blood (% Dose Estimated Total Blood Volume/Hr.)
<i>Control Group</i>		
11:52	0.3	0.4
8:53	1.8	3.5
11:53	0.8	1.4
19:53	0.9	2.5
8:54	0.85	4.8
9:54	0.8	4.3
Mean ..	0.9 ± 0.2	2.8 ± 0.7
<i>Transected Rabbits</i>		
13:53	0	1.4
20:53	0	0.7
21:53	0	0.6
11:54	0	0.45
17:54	0	1.2
Mean ..	0	0.87 ± 0.19

The blood volumes of the rabbits were estimated on a weight basis from the data of Armin and Grant (1951).

and it is concluded that: (1) In normal rabbits there is a delay in time following the injection of R.P.P. before its arrival in the blood is detected. This delay is of the same order of magnitude as that observed in normal human subjects (Table II). (2) In the transected rabbits R.P.P. could be detected in the blood immediately following the injection. (3) Despite the immediate appearance in the blood of detectable amounts of R.P.P. in the transected rabbits, the initial rate of rise of R.P.P. content in the blood was greater in normal animals.

Interpretation of Experimental Findings

The present concept of tissue fluid formation and absorption is based on the original hypothesis of Starling (1896), which described a hydrodynamic process governed by the outward filtration force of capillary hydrostatic pressure and the absorbing force developed by the osmotic pressure of the plasma proteins. This hydrodynamic process is slow and is concerned largely with the net volume flow of fluid. Pappenheimer (1953) has summarized evidence to indicate

that diffusion rather than hydrodynamic flow is the mechanism of molecular exchange between the blood plasma and interstitial fluid. Molecular diffusion is rapid, is independent of filtration or absorption, and can occur against the flow of bulk transference of fluid. Thus Hyman, Rapaport and Paldino (1952) found no significant difference in the clearance rate of radioactive iodide from normal skin and from skin in which outward filtration of fluid from the capillaries had been promoted by infiltration with a 12.5% protein solution.

Pappenheimer, Renkin, and Borrero (1951) have postulated that diffusion of water- and lipid-insoluble molecules takes place through channels or pores in the capillary wall. Although the diffusion rate of small molecules through these channels is rapid, it is slower than if free diffusion was taking place. This is explained by the concept of restricted diffusion, which becomes increasingly important as molecular size approaches the diameter of the channels through the capillary wall. Thus for large protein molecules, at normal filtration rates, a high degree of molecular sieving occurs, and the resulting filtrate or tissue fluid contains small quantities of protein only. This protein leak into the tissue spaces is small, and is not sufficient to disturb the osmotic relationship on which the Starling hypothesis depends.

The fate of this extravascular protein is obscure, but it is generally held that the lymphatics offer no barrier to protein molecules and readily remove such protein as has reached the tissue space. This problem has been investigated previously by several workers. Field and Drinker (1931) injected horse serum subcutaneously into dogs and detected its presence in blood and lymph by serological methods. They found that after subcutaneous injection the protein found its way rapidly into the lymphatics and could be detected in the cervical lymph trunks after 30 minutes. When lymphatic entrance into the blood stream was prevented by ligation of the thoracic and cervical lymph ducts, the foreign protein could not be detected in the blood stream for periods of up to seven hours. Similar results were reported by Lewis (1921) and Conklin (1930).

Jepson, Simeone, and Dobyns (1953) investigated the fate of R.P.P. injected intradermally in dogs and reached the conclusion that absorption through blood capillaries was the major factor in removal of the protein. Their experiments differed from those reported here in that the R.P.P. was injected into the skin itself instead of subcutaneously, and it may be that the higher pressure required for such injections deranged the local physiological equilibrium, and permitted direct absorption into the blood capillaries.

In this investigation the disappearance of R.P.P. from the injection site in human subjects shows a tendency to be slower when the lymphatic circulation is impaired. The lack of differentiation between the R.P.P. removal rates observed in transected and control animals is probably caused, among other factors, by diffusion of the R.P.P. into the oedema of the transected limb, which makes the removal rates appear too high. A further effect which would make the observed removal rate too high in the transected animals would be produced if the lymphatics were able to carry R.P.P. away from the injection site, only to discharge it through their cut ends into the oedema fluid at the transection. This possibility is supported by the higher activity observed in the tissue specimens which were taken from just below the transection.

The time and rate of appearance of R.P.P. in the blood can be interpreted in terms of the mechanism by which the R.P.P. is removed from the injection site. The two possible removal mechanisms to be considered are: (1) passage of R.P.P. from the tissue fluids directly into the blood, through the capillary walls; and (2) absorption of R.P.P. into the lymphatic system with its subsequent discharge into the blood system. If the former mechanism only were operative the R.P.P. would appear in the blood immediately after its subcutaneous injection and the rate of increase of the R.P.P. content of the blood would be the highest at the initial stage. The magnitude of this rate of increase would be directly

related to the rate of passage of R.P.P. back through the capillary walls. The second mechanism, on the other hand, would involve some delay after the injection before the R.P.P. content of the blood began to rise, corresponding to the time it takes for the R.P.P. to pass through the lymphatic system and hence into the blood stream. Longer delays would be associated with slower functioning of the lymphatic system, and it might be expected that the subsequent rate of increase of R.P.P. in the blood would be correspondingly slower.

With the exception of the result for the transected animals the variation of R.P.P. in the blood has followed the pattern expected from the second mechanism. In human subjects the initial delay is longer and the initial rate of increase of R.P.P. in the blood is much smaller in the patients with severe lymphoedema than in the control group of normal subjects. In the latter the observed values are also related to the degree of physical activity. It appears, therefore, that in the cases examined the lymphatic system is the most important mechanism for the transport of proteins from the tissue fluids. The iodide contamination of our R.P.P. made it, unfortunately, impossible to decide whether there is a return of a small proportion of protein directly to the blood through the capillary walls.

The transected animals are the only group in which blood absorption of R.P.P. appears to be taking place. Here the lymphatic route is destroyed and the normal physiological conditions are disturbed by trauma so that appreciable passage of R.P.P. in the reverse direction through the capillary walls becomes possible. Even in these conditions the removal of protein from the tissue, as measured by the initial rate of increase of R.P.P. in the blood, is considerably (about three times) slower than in the control animals.

The results of this investigation indicate that the behaviour of R.P.P. injected subcutaneously can be used as a test of lymphatic function. The method is useful as a research tool, but it is too expensive and time-consuming for routine clinical purposes.

Summary and Conclusions

The absorption of plasma protein labelled with radioactive iodine (R.P.P.) from the subcutaneous tissues has been studied in normal subjects and in patients suffering from lymphoedema. A similar investigation was performed in normal rabbits and in rabbits with a limb in which lymphatic transection had been performed.

The behaviour of radioactive plasma protein injected subcutaneously in the limbs of human subjects and animals is consistent with its removal by the lymphatic route.

Detachable direct absorption of protein into the blood stream occurred only after acute traumatic destruction of the lymphatic pathway.

The rate of removal of R.P.P. is slower in patients with severe lymphoedema than in normal subjects.

In normal subjects the rate of removal of R.P.P. is hastened by exercise.

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CASE OF REVERSE COARCTATION SYNDROME

AN AORTIC ARCH SYNDROME

BY

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The interesting clinical syndrome characterized by absence of pulsation in the arteries arising from the arch of the aorta, though very rare, has been reported from time to time. In this condition one or more of these arteries are involved in an obliterative process. A large variety of pathological lesions may be responsible for such arterial occlusion. Of these, a primary panarteritis of unknown aetiology is in a class by itself, and has been variously described as 'Takayasu's disease,' 'pulseless disease,' and 'young female arteritis.'

The largest series of pulseless disease seems to have been reported from Japan, and a comprehensive list of 58 cases was given by Caccamise and Whitman (1952) along with the report of their own case. Skipper and Flint (1952) summarized 16 cases of 'syphilitic' and 'non-syphilitic' origin and recorded two non-syphilitic cases of their own. Ross and McKusick (1953), in an extensive review of the world literature, analysed over 100 cases, 35 being previously unreported. They discussed the whole subject of pulse anomalies in the branches of the aortic arch under the title 'aortic arch syndrome,' a term first suggested by Frovig in 1946. Other possible aetiological factors besides the panarteritis, according to their analysis, are syphilis and trauma, with or without aneurysm formation, chronic dissection of the aorta, atheromatosis, congenital anomalies, mediastinal tumours, and thrombophilia. They concluded that syphilis is the commonest and primary atheroma a very rare cause of aortic arch syndrome.

Recently two more cases of 'pulseless disease' have been reported in the Anglo-American press (Barker and Edwards, 1955; Trias de Bes *et al.*, 1955). From India the first case of aortic arch syndrome was published by Shikhare (1921), and so far as we know the case reported below is the second. Our case is of interest not only because the syndrome itself is rare but also because it belongs to a very rare aetiological variety.

Case Report

A sweeper of a veterinary hospital, aged 51, was admitted to hospital complaining of low pyrexia, breathlessness, productive cough, and generalized body ache of ten days' duration. He had been a chronic sufferer from productive cough for a long time, with occasional exacerbations, especially in the winter months, but his activities had not previously been limited by breathlessness. He had occasional attacks of vertigo, though they were never very severe. A hospital discharge ticket in his possession showed that he was sent home a fortnight previously after successful treatment of a hypopyon ulcer of his right eye.

The patient was thinly built and looked very ill, with sunken eyes and cheeks. Bilateral lenticular opacity and a scar on the lower part of the right cornea were present. The fundus oculi could not be properly visualized because of the lens opacities. The palpebral conjunctiva looked rather pale. He was slightly cyanosed; the respiratory rate was 42 a minute. Clinically the chest was grossly emphysematous. The breath sound was vesicular in character with